

We claim:

1. A method of modulating insulin activity in mammalian cells, said method comprising administering to said cells an amino acid sequence which binds IR and comprises the amino acid sequence  $X_1X_2X_3X_4X_5$ , wherein  $X_1$ ,  $X_2$ ,  $X_4$ , and  $X_5$  are aromatic amino acids, and  $X_3$  is any polar amino acid.
2. The method according to claim 1 wherein  $X_1$ ,  $X_2$ , and  $X_5$  are selected from the group consisting of phenylalanine and tyrosine,  $X_3$  is selected from the group consisting of aspartic acid, glutamic acid, glycine and serine, and  $X_4$  is selected from group consisting of tryptophan, tyrosine and phenylalanine.
3. The method according to claim 2 wherein said amino acid sequence is an insulin agonist.
4. The method according to claim 2 wherein said amino acid sequence is an insulin antagonist.
5. The method according to claim either one of claims 3 or 4 wherein  $X_1$  and  $X_5$  are phenylalanine and  $X_2$  is tyrosine.
6. The method according to claim 5 wherein  $X_4$  is tryptophan.
7. The method according to claim 6 wherein the amino acid sequence is an insulin agonist and  $X_3$  is selected from the group consisting of aspartic acid and glutamic acid.

8. (Once Amended) The method according to claim 7 wherein  $X_3$  is aspartic acid to result in an amino acid sequence comprising FYDWF (SEQ ID NO: 2411).
9. (Once Amended) The method according to claim 7 wherein  $X_3$  is glutamic acid to result in an amino acid sequence comprising FYEWF (SEQ ID NO: 2412).
10. (Once Amended) The method according to claim 1 wherein the amino acid sequence FHEN (SEQ ID NO: 2633) is bound to the amino terminal of  $X_1X_2X_3X_4X_5$  to produce an amino acid sequence comprising FHEN $X_1X_2X_3X_4X_5$  (SEQ ID NO: 2634) and possessing insulin agonist activity.
11. (Once Amended) The method according to claim 10 wherein the amino acid sequence is FHENFYDWF (SEQ ID NO: 2635).
12. The method according to claim 1 wherein the amino acid sequence  $X_1X_2X_3X_4X_5$  further comprises the amino acid sequence  $X_{93} X_{94} X_{95} X_{96} X_{97}$  located at the carboxy terminal end adjacent to  $X_5$ , wherein  $X_{93}$ ,  $X_{94}$  and  $X_{97}$  may be any amino acid,  $X_{95}$  is selected from the group consisting of glutamine, glutamic acid, alanine and lysine, and  $X_{96}$  is a hydrophobic or aliphatic amino acid.
13. The method according to claim 12 wherein  $X_{93}$  is selected from the group consisting of alanine, aspartic acid, glutamic acid, arginine, and valine,  $X_{95}$  is glutamine or glutamic acid, and  $X_{96}$  is selected from the group consisting of leucine, isoleucine, valine and tryptophan.

14. The method according to claim 13 wherein X<sub>96</sub> is leucine or tryptophan.
15. The method according to claim 14 wherein X<sub>96</sub> is leucine.
16. The method according to claim 13 wherein X<sub>95</sub> is glutamine or glutamic acid, and X<sub>96</sub> is tryptophan.
17. The method according to claim 13 wherein X<sub>95</sub> is glutamic acid and the amino acid sequence is an insulin agonist.
18. (Once Amended) The method according to claim 13 wherein asparagine is present as the amino acid bound to the amino terminal of X<sub>1</sub> and wherein X<sub>1</sub>X<sub>2</sub>X<sub>3</sub>X<sub>4</sub>X<sub>5</sub>X<sub>93</sub> is FYDWFV (SEQ ID NO: 2636).
19. The method according to claim 1 wherein the amino acid sequence is selected from the group of amino acid sequences listed in Figures 1, 2, and 9.
20. (Once Amended) The method according to claim 1 wherein the sequence is selected from the group consisting of FHENFYDWFVRQVSK (SEQ ID NO: 2115), DYKDVTFSTSAVFHENFYDWFVRQVSKK (SEQ ID NO: 2111), GRVDWLQRNANFYDWFVAELG (SEQ ID NO: 2163) and APTFYAWFNQQT (SEQ ID NO: 1870).
21. (Once Amended) The method according to claim 1 wherein the sequence is selected from the group consisting of FHENFYDWFVRQVAKK-NH<sub>2</sub> (SEQ ID NO: 2447) FHENFYDWFVRQASKK-NH<sub>2</sub> (SEQ ID NO: 2448)

FHENFYDWFVRAVSKK-NH<sub>2</sub> (SEQ ID NO: 2449)  
FHENFYDWFVAQVSKK-NH<sub>2</sub> (SEQ ID NO: 2450)  
FHENFYDWFARQVSKK-NH<sub>2</sub> (SEQ ID NO: 2451)  
FHEAFYDWFVRQVSKK-NH<sub>2</sub> (SEQ ID NO: 2452)  
FHANFYDWFVRQVSKK-NH<sub>2</sub> (SEQ ID NO: 2453)  
FAENFYDWFVRQVSKK-NH<sub>2</sub> (SEQ ID NO: 2454)  
AHENFYDWFVRQVSKK-NH<sub>2</sub> (SEQ ID NO: 2455)  
fhenfydwfvrqvsck (SEQ ID NO: 2456)  
EFHENFYDWFVRQVSEE (SEQ ID NO: 2457)  
FHENFYGWFVRQVSKK (SEQ ID NO: 2458)  
HETFYSMIRSLAK (SEQ ID NO: 2459)  
SDGFYNAIELLS (SEQ ID NO: 2460)  
SLNFYDALQLLAKK (SEQ ID NO: 2461)  
HDPFYSMMSLLK (SEQ ID NO: 2462)  
NSFYEARMLSSK (SEQ ID NO: 2463)  
HPTSKEIYAKLLK (SEQ ID NO: 2464)  
HPSTNQMLMKLFK (SEQ ID NO: 2465)  
HPPLSELKLFLIKK (SEQ ID NO: 2466)  
HAPLSVLVQALLKK (SEQ ID NO: 2467)  
HPSLSDMRWILLK (SEQ ID NO: 2468)  
WSDFYSYFQGLD (SEQ ID NO: 2469)  
D117-Dap(D117) (SEQ ID NO: 2470)  
SSNFYQALMLLS (SEQ ID NO: 2471)  
D117-Dap(CO-CH<sub>2</sub>-O-NH<sub>2</sub>) (SEQ ID NO: 2472)  
HENFYGWFVRQVSKK (SEQ ID NO: 2473)  
D117-Lys(D117) (SEQ ID NO: 2474)  
D117-b-Ala-Lys(D117) (SEQ ID NO: 2475)  
D117-b-Ala-Dap(b-Ala-D117) (SEQ ID NO: 2476)  
D117-Gly-Lys(Gly-D117) (SEQ ID NO: 2477)  
D117-b-Ala-Lys(b-Ala-D117) (SEQ ID NO: 2478)  
D117-Dab(D117) (SEQ ID NO: 2479)  
D117-Orn(D117) (SEQ ID NO: 2480)  
D117-Dap(b-Ala-D117) (SEQ ID NO: 2481)  
D117-b-Ala-Orn(b-Ala-D117) (SEQ ID NO: 2482)  
1-(Thia-b-Ala-D117)<sub>2</sub> (SEQ ID NO: 2483)  
FHENFYDWFVRQVS (SEQ ID NO: 2484)  
FHENFYDWFVRQVSK (SEQ ID NO: 2485)  
FHENFYDWFVQVSK (SEQ ID NO: 2486)  
FHENFYDWFVVS (SEQ ID NO: 2487)  
FHENFYDWFVSK (SEQ ID NO: 2488)

FHENFYDWFVK (SEQ ID NO: 2489)  
FYDWF-NH<sub>2</sub> (SEQ ID NO: 2490)  
FYDWFKK-NH<sub>2</sub> (SEQ ID NO: 2491)  
AFYDWFACK-NH<sub>2</sub> (SEQ ID NO: 2160)  
AAAAFYDWFAAAAKK-NH<sub>2</sub> (SEQ ID NO: 2492)  
(D117)<sub>2-12</sub> (SEQ ID NO: 2493)  
(Cys-Gly-D117)<sub>2</sub> (SEQ ID NO: 2494)  
Cys-Gly-D117 (SEQ ID NO: 2495)  
(D117)<sub>2-14</sub> (SEQ ID NO: 2496)  
LDALDRLMRYFEERPSL-NH<sub>2</sub> (SEQ ID NO: 2461)  
PLAELWAYFEHSEQGRSSAH-NH<sub>2</sub> (SEQ ID NO: 2462)  
GRVDWLQRNANFYDWFVAELG-NH<sub>2</sub> (SEQ ID NO: 2463)  
NGVERAGTGDNFYDWFVAQLH-NH<sub>2</sub> (SEQ ID NO: 2464)  
EHWNTVDPFYFTLFEWLRESG-NH<sub>2</sub> (SEQ ID NO: 2465)  
EHWNTVDPFYQYFSELLRESG-NH<sub>2</sub> (SEQ ID NO: 2466)  
QSDSGTVHDRFYGWFRDTWAS-NH<sub>2</sub> (SEQ ID NO: 2467)  
AFYDWFACK-NH<sub>2</sub> (SEQ ID NO: 2497)  
AFYDWFANH<sub>2</sub> (SEQ ID NO: 2498)  
AFYDWF-NH<sub>2</sub> (SEQ ID NO: 2499)  
FYDWDANH<sub>2</sub> (SEQ ID NO: 2500)  
Ac-FYDWF-NH<sub>2</sub> (SEQ ID NO: 2501)  
Lig-FHENFYDWFVRQVSKK (SEQ ID NO: 2502)  
Lig-GGGFHENFYDWFVRQVSKK (SEQ ID NO: 2503)  
FHENFYDWFVRQVSKKGGG-Lig (SEQ ID NO: 2504)  
Lig-CAWPTYWNCG (SEQ ID NO: 2505)  
ACAWPTYWNCG-Lig (SEQ ID NO: 2506)  
ACAWPTYWNCGGGG-Lig (SEQ ID NO: 2507)  
Lig-SDGFYNAIELLS (SEQ ID NO: 2508)  
SDGFYNAIELLS-Lig (SEQ ID NO: 2509)  
SDGFYNAIELLSGGG-Lig (SEQ ID NO: 2510)  
KHLCVLEELFWGASLFGYCSGKK-Lig (SEQ ID NO: 2511)  
AFYDWFACK-Lig (SEQ ID NO: 2512)  
AFYEWFAKK-NH<sub>2</sub> (SEQ ID NO: 2513)  
AFYGWFAKK-NH<sub>2</sub> (SEQ ID NO: 2514)  
AFYKWFAKK-NH<sub>2</sub> (SEQ ID NO: 2515)  
(SDGFYNAIELLS-Lig)<sub>2-14</sub> (SEQ ID NO: 2516)  
(AFYDWFACK-Lig)<sub>2-14</sub> (SEQ ID NO: 2517)  
FHENAYDWFVRQVSKK (SEQ ID NO: 2518)  
FHENFADWFVRQVSKK (SEQ ID NO: 2519)  
FHENFYAWFVRQVSKK (SEQ ID NO: 2520)

FHENFYDAFVRQVSKK (SEQ ID NO: 2521)  
FHENFTDWAVRQVSKK (SEQ ID NO: 2522)  
FQSLLEELVWGAPLFRYGTG (SEQ ID NO: 2523)  
PLCVLEELFWGASLFGQCSG (SEQ ID NO: 2524)  
QLEEEWAGVQCEVYGRECPs (SEQ ID NO: 2525)  
Cys-(Gly)<sub>2</sub>-D117 (SEQ ID NO: 2526)  
(Cys-(Gly)<sub>2</sub>-D117)<sub>2</sub> (SEQ ID NO: 2527)  
(S210)-14-(S212) (SEQ ID NO: 2528)  
(S131)-14-(S212) (SEQ ID NO: 2529)  
(S205)<sub>2</sub>-14 (SEQ ID NO: 2530)  
(S204)<sub>2</sub>-14 (SEQ ID NO: 2531)  
(S131)-14-(S210) (SEQ ID NO: 2532)  
RVDWLQRNANFYDWFVAELG (SEQ ID NO: 2533)  
VDWLQRNANFYDWFVAELG (SEQ ID NO: 2534)  
DWLQRNANFYDWFVAELG (SEQ ID NO: 2535)  
WLQRNANFYDWFVAELG (SEQ ID NO: 2536)  
LQRNANFYDWFVAELG (SEQ ID NO: 2537)  
QRNANFYDWFVAELG (SEQ ID NO: 2538)  
RNANFYDWFVAELG (SEQ ID NO: 2539)  
NANFYDWFVAELG (SEQ ID NO: 2540)  
ANFYDWFVAELG (SEQ ID NO: 2541)  
NFYDWFVAELG (SEQ ID NO: 2542)  
GRVDWLQRNANFYDWFVAELG-Lig (SEQ ID NO: 2543)  
Lig-GRVDWLQRNANFYDWFVAELG (SEQ ID NO: 2544)  
(S208)-14-(S131) (SEQ ID NO: 2545)  
(S208)-14-(S209) (SEQ ID NO: 2546)  
GRVDWLQRNANFYDWFVAEL (SEQ ID NO: 2547)  
GRVDWLQRNANFYDWFVAE (SEQ ID NO: 2548)  
GRVDWLQRNANFYDWFVA (SEQ ID NO: 2549)  
GRVDWLQRNANFYDWFV (SEQ ID NO: 2550)  
14-(SDGFYNAIELLS-Lig)<sub>2</sub> (SEQ ID NO: 2551)  
(GRVDWLQRNANFYDWFVAELG)-14 (SEQ ID NO: 2552)  
14-(GRVDWLQRNANFYDWFVAE LG) (SEQ ID NO: 2553)  
(SDGFYNAIELLSGGG)<sub>2</sub>-14 (SEQ ID NO: 2554)  
H-Acy-CLEE-w-GASL-Tic-QCSG-NH<sub>2</sub> (SEQ ID NO: 2555)  
RWPNFYGYFESLLTHFS-NH<sub>2</sub> (SEQ ID NO: 2172)  
HYNAFYEYFQVLLAETW-NH<sub>2</sub> (SEQ ID NO: 2173)  
EGWDFYSYFSGLLASVT-NH<sub>2</sub> (SEQ ID NO: 2174)  
LDRQFYRYFQDLLVGFM-NH<sub>2</sub> (SEQ ID NO: 2556)  
WGRSFYRYFETLLAQGI-NH<sub>2</sub> (SEQ ID NO: 2557)

PLCFLQELFGGASLGGYCSG-NH<sub>2</sub> (SEQ ID NO: 2558)  
WLEQERAWIWCEIQGSGCRA-NH<sub>2</sub> (SEQ ID NO: 2559)  
IQGWEPFYGWFDVVAQMFEE-NH<sub>2</sub> (SEQ ID NO: 2171)  
TGHRGLGLDEQFYWWFRDALSG-NH<sub>2</sub> (SEQ ID NO: 2560)  
H-Abu-CLEE-w-GASL-Tic-QCSG-NH<sub>2</sub> (SEQ ID NO: 2561)  
14-(Dap-CAWPTYWNCG)<sub>2</sub> (SEQ ID NO: 2562)  
RDHypFYDWFDDi-NH<sub>2</sub> (SEQ ID NO: 2563)  
S131-14-S209 (SEQ ID NO: 2564)  
S294-14-S210 (SEQ ID NO: 2565)  
S295-14-S210 (SEQ ID NO: 2566)  
S294-14-204 (SEQ ID NO: 2567)  
S295-14-S204 (SEQ ID NO: 2568)  
GFREGQRWYWFVAQVT-NH<sub>2</sub> (SEQ ID NO: 246)  
VASGHVLHGQFYRWFVDQFALEE-NH<sub>2</sub> (SEQ ID NO: 2569)  
VGDFCVSHDCFYGWFLRESMQ-NH<sub>2</sub> (SEQ ID NO: 2570)  
DLRVLCELFGGAYVLGYCSE-NH<sub>2</sub> (SEQ ID NO: 2571)  
HLSVGEELSWWVALLGQWAR-NH<sub>2</sub> (SEQ ID NO: 2572)  
APVSTEELRWGALLFGQWAG-NH<sub>2</sub> (SEQ ID NO: 2573)  
ALEEEWAWVQVRSIRSGLPL-NH<sub>2</sub> (SEQ ID NO: 2574)  
WLEHEWAQIQCELYGRGCTY-NH<sub>2</sub> (SEQ ID NO: 2575)  
AAVHEQFYDWFADQYEE-NH<sub>2</sub> (SEQ ID NO: 2576)  
QAPSNFYDWFVREWDEE-NH<sub>2</sub> (SEQ ID NO: 2577)  
QSFYDYIEELLGGEWKK-NH<sub>2</sub> (SEQ ID NO: 2578)  
DPFYQGLWEWLRESGEE-NH<sub>2</sub> (SEQ ID NO: 2579)  
(S204)<sub>2</sub>-7 (SEQ ID NO: 2580)  
(S204)<sub>2</sub>-9 (SEQ ID NO: 2581)  
(S204)<sub>2</sub>-12 (SEQ ID NO: 2582)  
(S204)<sub>2</sub>-13 (SEQ ID NO: 2583)  
DWLQRNANFYDWFVAEL-Lig (SEQ ID NO: 2584)  
Lig-DWLQRNANFYDWFVAEL (SEQ ID NO: 2585)  
(S209)<sub>2</sub>-9 (SEQ ID NO: 2586)  
(S210)<sub>2</sub>-9 (SEQ ID NO: 2587)  
LigKHLCVLEELFWGASLFGYCSGKKKK (SEQ ID NO: 2588)  
KHLCVLEELFWGASLFGYCSGKKKK-Lig (SEQ ID NO: 2589)  
(S294)<sub>2</sub>-14 (SEQ ID NO: 2590)  
(S295)<sub>2</sub>-14 (SEQ ID NO: 2591)  
S-D-G-F-Y-N-A-Acy-E-L-L-S (SEQ ID NO: 2592)  
S-G-P-F-Y-E-E-Acy-E-L-L-W-Aib (SEQ ID NO: 2593)  
G-G-S-F-Y-D-D-Acy-E-Aib-L-W-Aib (SEQ ID NO: 2594)  
N-Aib-P-F-Y-D-E-Acy-D-E-Cha-W-Aib (SEQ ID NO: 2595)

GRVDWLQRNANFYDWFVAEAcyG-NH<sub>2</sub> (SEQ ID NO: 2596)  
and wherein underlined numbers represent a linker as defined in

Table 18.

22. The method according to claim 2 wherein the amino acid sequence binds to the insulin receptor with an affinity of at least about  $10^{-5}$  M.
23. The method according to claim 22 wherein the affinity is at least about  $10^{-7}$  M.
24. The method according to claim 23 wherein the affinity is at least about  $10^{-9}$  M.
25. An amino acid sequence comprising  $X_1X_2X_3X_4X_5$  wherein  $X_1$ ,  $X_2$ ,  $X_4$ , and  $X_5$  are aromatic amino acids,  $X_3$  is any polar amino acid, and wherein said amino acid sequence binds to IGF-1R.
26. The amino acid sequence according to claim 25 wherein the IGF-1R binding occurs with an affinity ( $K_d$ ) of at least about  $10^{-5}$  M.
27. The amino acid sequence according to claim 25 wherein the binding occurs at an affinity ( $K_d$ ) of at least about  $10^{-7}$  M.
28. The amino acid sequence according to claim 25 wherein  $X_1$ ,  $X_2$ , and  $X_5$  are selected from the group consisting of phenylalanine and tyrosine,  $X_3$  is selected from the group consisting of aspartic acid, glutamic acid, glycine and serine, and  $X_4$  is selected from group consisting of tryptohpan, tyrosine and phyenylalanine.



29. The amino acid sequence according to claim 28 wherein  $X_3$  is selected from the group consisting of aspartic acid and glutamic acid.
30. The amino acid sequence according to claim 29 wherein  $X_1$  and  $X_5$  are phenylalanine and  $X_2$  is tyrosine.
31. The amino acid sequence according to claim 29 wherein  $X_4$  is tryptophan.
32. (Once Amended) The amino acid sequence according to claim 31 wherein  $X_3$  is aspartic acid to result in an amino acid sequence comprising FYDWF (SEQ ID NO: 2411).
33. (Once Amended) The amino acid sequence according to claim 31 wherein  $X_3$  is glutamic acid to result in an amino acid sequence comprising FYEWF (SEQ ID NO: 2412).
34. (Once Amended) The amino acid sequence according to claim 28 wherein the amino acid sequence FHEN (SEQ ID NO: 2633) is bound to the amino terminal of  $X_1X_2X_3X_4X_5$  to produce an amino acid sequence comprising FHEN $X_1X_2X_3X_4X_5$  (SEQ ID NO: 2634).
35. (Once Amended) The amino acid sequence according to claim 34 wherein the amino acid sequence comprises FHENFYDWF (SEQ ID NO: 2635).

36. The amino acid sequence according to claim 25 wherein the amino acid sequence  $X_1X_2X_3X_4X_5$  further comprises the amino acid sequence  $X_{93} X_{94} X_{95} X_{96} X_{97}$  located at the carboxy terminal end adjacent to  $X_5$  to form  $X_1X_2X_3X_4X_5X_{93}X_{94}X_{95}X_{96}X_{97}$ , wherein  $X_{93}$ ,  $X_{94}$  and  $X_{97}$  may be any amino acid,  $X_{95}$  is selected from the group consisting of glutamine, glutamic acid, alanine and lysine, and  $X_{96}$  is a hydrophobic or aliphatic amino acid.
37. The amino acid sequence according to claim 36 wherein  $X_{93}$  is selected from the group consisting of alanine, aspartic acid, glutamic acid, arginine, and valine,  $X_{95}$  is glutamine or glutamic acid, and  $X_{96}$  is selected from the group consisting of leucine, isoleucine, valine and tryptophan.
38. The amino acid sequence according to claim 37 wherein  $X_{96}$  is leucine or tryptophan.
39. The amino acid sequence according to claim 38 wherein  $X_{96}$  is leucine.
40. The amino acid sequence according to claim 39 wherein  $X_{95}$  is glutamine, and  $X_{96}$  is tryptophan.
41. The amino acid sequence according to claim 40 wherein  $X_{93}$  is valine.
42. The amino acid sequence according to claim 41 wherein asparagine is bound to the amino terminal of  $X_1$ .
43. An amino acid sequence selected from the amino acid sequences listed in Figures 1-A through 1-O.

44. (Once Amended) The amino acid sequence according to claim 25 wherein the sequence is selected from the group consisting of FHENFYDWFVRQVS (SEQ ID NO: 2115), DYKDVTFTSAVFHENFYDWFVRQVSKK (SEQ ID NO: 2111), GRVDWLQRNANFYDWFVAELG (SEQ ID NO: 2163) and APTFYAWFNQQT (SEQ ID NO: 1870).
45. (Once Amended) The amino acid sequence according to claim 25 wherein the sequence comprises FHENFYDWFVRQVS (SEQ ID NO: 2115).
46. (Once Amended) The amino acid sequence according to claim 25 wherein the sequence is selected from the group consisting of
- FHENFYDWFVRQVAKK-NH<sub>2</sub> (SEQ ID NO: 2447)  
FHENFYDWFVRQASKK-NH<sub>2</sub> (SEQ ID NO: 2448)  
FHENFYDWFVRAVSKK-NH<sub>2</sub> (SEQ ID NO: 2449)  
FHENFYDWFVAQVSKK-NH<sub>2</sub> (SEQ ID NO: 2450)  
FHENFYDWFARQVSKK-NH<sub>2</sub> (SEQ ID NO: 2451)  
FHEAFYDWFVRQVSKK-NH<sub>2</sub> (SEQ ID NO: 2452)  
FHANFYDWFVRQVSKK-NH<sub>2</sub> (SEQ ID NO: 2453)  
FAENFYDWFVRQVSKK-NH<sub>2</sub> (SEQ ID NO: 2454)  
AHENFYDWFVRQVSKK-NH<sub>2</sub> (SEQ ID NO: 2455)  
fhenfydwfvrqvskk (SEQ ID NO: 2456)  
EFHENFYDWFVRQVSEE (SEQ ID NO: 2457)  
FHENFYGWVVRQVSKK (SEQ ID NO: 2458)  
HETFYSMIRSLAK (SEQ ID NO: 2459)  
SDGFYNAIELLS (SEQ ID NO: 2460)  
SLNFYDALQLLAKK (SEQ ID NO: 2461)  
HDPFYMMKSLLK (SEQ ID NO: 2462)  
NSFYEARMLSSK (SEQ ID NO: 2463)  
HPTSKEIYAKLLK (SEQ ID NO: 2464)  
HPSTNQMLMKLFFK (SEQ ID NO: 2465)  
HPPLSELKLFLIKK (SEQ ID NO: 2466)  
HAPLSVLVQALLKK (SEQ ID NO: 2467)  
HPSLSDMRWILLK (SEQ ID NO: 2468)

WSDFYSYFQGLD (SEQ ID NO: 2469)  
D117-Dap(D117) (SEQ ID NO: 2470)  
SSNFYQALMLLS (SEQ ID NO: 2471)  
D117-Dap(CO-CH<sub>2</sub>-O-NH<sub>2</sub>) (SEQ ID NO: 2472)  
HENFYGWFVRQVSKK (SEQ ID NO: 2473)  
D117-Lys(D117) (SEQ ID NO: 2474)  
D117-b-Ala-Lys(D117) (SEQ ID NO: 2475)  
D117-b-Ala-Dap(b-Ala-D117) (SEQ ID NO: 2476)  
D117-Gly-Lys(Gly-D117) (SEQ ID NO: 2477)  
D117-b-Ala-Lys(b-Ala-D117) (SEQ ID NO: 2478)  
D117-Dab(D117) (SEQ ID NO: 2479)  
D117-Orn(D117) (SEQ ID NO: 2480)  
D117-Dap(b-Ala-D117) (SEQ ID NO: 2481)  
D117-b-Ala-Orn(b-Ala-D117) (SEQ ID NO: 2482)  
1-(Thia-b-Ala-D117)<sub>2</sub> (SEQ ID NO: 2483)  
FHENFYDWFVRQVS (SEQ ID NO: 2484)  
FHENFYDWFVRQVSK (SEQ ID NO: 2485)  
FHENFYDWFVQVSK (SEQ ID NO: 2486)  
FHENFYDWFVVS (SEQ ID NO: 2487)  
FHENFYDWFVSK (SEQ ID NO: 2488)  
FHENFYDWFVK (SEQ ID NO: 2489)  
FYDWF-NH<sub>2</sub> (SEQ ID NO: 2490)  
FYDWFKK-NH<sub>2</sub> (SEQ ID NO: 2491)  
AFYDWFKK-NH<sub>2</sub> (SEQ ID NO: 2160)  
AAAAFYDWFAAAAKK-NH<sub>2</sub> (SEQ ID NO: 2492)  
(D117)<sub>2-12</sub> (SEQ ID NO: 2493)  
(Cys-Gly-D117)<sub>2</sub> (SEQ ID NO: 2494)  
Cys-Gly-D117 (SEQ ID NO: 2495)  
(D117)<sub>2-14</sub> (SEQ ID NO: 2496)  
LDALDRLMRYFEERPSL-NH<sub>2</sub> (SEQ ID NO: 2461)  
PLAELWAYFEHSEQGRSSAH-NH<sub>2</sub> (SEQ ID NO: 2462)  
GRVDWLQRNANFYDWFVAELG-NH<sub>2</sub> (SEQ ID NO: 2463)  
NGVERAGTGDNFYDWFVAQLH-NH<sub>2</sub> (SEQ ID NO: 2464)  
EHWNTVDPFYFTLFEWLRESG-NH<sub>2</sub> (SEQ ID NO: 2465)  
EHWNTVDPFYQYFSELLRESG-NH<sub>2</sub> (SEQ ID NO: 2466)  
QSDSGTVHDRFYGWFRDTWAS-NH<sub>2</sub> (SEQ ID NO: 2467)  
AFYDWFKK-NH<sub>2</sub> (SEQ ID NO: 2497)  
AFYDWF-NH<sub>2</sub> (SEQ ID NO: 2498)  
AFYDWF-NH<sub>2</sub> (SEQ ID NO: 2499)  
FYDWD-NH<sub>2</sub> (SEQ ID NO: 2500)

Ac-FYDWF-NH<sub>2</sub> (SEQ ID NO: 2501)  
Lig-FHENFYDWFVRQVSKK (SEQ ID NO: 2502)  
Lig-GGGFHENFYDWFVRQVSKK (SEQ ID NO: 2503)  
FHENFYDWFVRQVSKKGGG-Lig (SEQ ID NO: 2504)  
Lig-CAWPTYWNCG (SEQ ID NO: 2505)  
ACAWPTYWNCG-Lig (SEQ ID NO: 2506)  
ACAWPTYWNCGGGG-Lig (SEQ ID NO: 2507)  
Lig-SDGFYNAIELLS (SEQ ID NO: 2508)  
SDGFYNAIELLS-Lig (SEQ ID NO: 2509)  
SDGFYNAIELLSGGG-Lig (SEQ ID NO: 2510)  
KHLCVLEELFWGASLFGYCSGKK-Lig (SEQ ID NO: 2511)  
AFYDWFACK-Lig (SEQ ID NO: 2512)  
AFYEWFAKK-NH<sub>2</sub> (SEQ ID NO: 2513)  
AFYGWFAKK-NH<sub>2</sub> (SEQ ID NO: 2514)  
AFYKWFAKK-NH<sub>2</sub> (SEQ ID NO: 2515)  
(SDGFYNAIELLS-Lig)<sub>2</sub>-14 (SEQ ID NO: 2516)  
(AFYDWFACK-Lig)<sub>2</sub>-14 (SEQ ID NO: 2517)  
FHENAYDWFVRQVSKK (SEQ ID NO: 2518)  
FHENFADWFVRQVSKK (SEQ ID NO: 2519)  
FHENFYAWFVRQVSKK (SEQ ID NO: 2520)  
FHENFYDAFVRQVSKK (SEQ ID NO: 2521)  
FHENFTDWAVRQVSKK (SEQ ID NO: 2522)  
FQSLLEELVWGAPLFRYGTG (SEQ ID NO: 2523)  
PLCVLEELFWGASLFGQCSG (SEQ ID NO: 2524)  
QLEEEWAGVQCEVYGRECPS (SEQ ID NO: 2525)  
Cys-(Gly)<sub>2</sub>-D117 (SEQ ID NO: 2526)  
(Cys-(Gly)<sub>2</sub>-D117)<sub>2</sub> (SEQ ID NO: 2527)  
(S210)-14-(S212) (SEQ ID NO: 2528)  
(S131)-14-(S212) (SEQ ID NO: 2529)  
(S205)<sub>2</sub>-14 (SEQ ID NO: 2530)  
(S204)<sub>2</sub>-14 (SEQ ID NO: 2531)  
(S131)-14-(S210) (SEQ ID NO: 2532)  
RVDWLQRNANFYDWFVAELG (SEQ ID NO: 2533)  
VDWLQRNANFYDWFVAELG (SEQ ID NO: 2534)  
DWLQRNANFYDWFVAELG (SEQ ID NO: 2535)  
WLQRNANFYDWFVAELG (SEQ ID NO: 2536)  
LQRNANFYDWFVAELG (SEQ ID NO: 2537)  
QRNANFYDWFVAELG (SEQ ID NO: 2538)  
RANFYDWFVAELG (SEQ ID NO: 2539)  
NANFYDWFVAELG (SEQ ID NO: 2540)

ANFYDWFVAELG (SEQ ID NO: 2541)  
NFYDWFVAELG (SEQ ID NO: 2542)  
GRVDWLQRNANFYDWFVAELG-Lig (SEQ ID NO: 2543)  
Lig-GRVDWLQRNANFYDWFVAELG (SEQ ID NO: 2544)  
(S208)-14-(S131) (SEQ ID NO: 2545)  
(S208)-14-(S209) (SEQ ID NO: 2546)  
GRVDWLQRNANFYDWFVAEL (SEQ ID NO: 2547)  
GRVDWLQRNANFYDWFVAE (SEQ ID NO: 2548)  
GRVDWLQRNANFYDWFVA (SEQ ID NO: 2549)  
GRVDWLQRNANFYDWFV (SEQ ID NO: 2550)  
14-(SDGFYNAIELLS-Lig)<sub>2</sub> (SEQ ID NO: 2551)  
(GRVDWLQRNANFYDWFVAELG)-14 (SEQ ID NO: 2552)  
14-(GRVDWLQRNANFYDWFVAE LG) (SEQ ID NO: 2553)  
(SDGFYNAIELLSGGG)<sub>2</sub>-14 (SEQ ID NO: 2554)  
H-Acy-CLEE-w-GASL-Tic-QCSG-NH<sub>2</sub> (SEQ ID NO: 2555)  
RWPNFYGYFESLLTHFS-NH<sub>2</sub> (SEQ ID NO: 2172)  
HYNAFYEFQVLLAETW-NH<sub>2</sub> (SEQ ID NO: 2173)  
EGWDFYSYFSGLLASVT-NH<sub>2</sub> (SEQ ID NO: 2174)  
LDRQFYRYFQDLLVGFM-NH<sub>2</sub> (SEQ ID NO: 2556)  
WGRSFYRYFETLLAQGI-NH<sub>2</sub> (SEQ ID NO: 2557)  
PLCFLQELFGGASLGGYCSG-NH<sub>2</sub> (SEQ ID NO: 2558)  
WLEQERAWIWCEIQGSGCRA-NH<sub>2</sub> (SEQ ID NO: 2559)  
IQGWEPFYGWFDVVAQMFEENH<sub>2</sub> (SEQ ID NO: 2171)  
TGHRLLGLDEQFYWWFRDALSG-NH<sub>2</sub> (SEQ ID NO: 2560)  
H-Abu-CLEE-w-GASL-Tic-QCSG-NH<sub>2</sub> (SEQ ID NO: 2561)  
14-(Dap-CAWPTYWNCG)<sub>2</sub> (SEQ ID NO: 2562)  
RDHypFYDWFDDi-NH<sub>2</sub> (SEQ ID NO: 2563)  
S131-14-S209 (SEQ ID NO: 2564)  
S294-14-S210 (SEQ ID NO: 2565)  
S295-14-S210 (SEQ ID NO: 2566)  
S294-14-204 (SEQ ID NO: 2567)  
S295-14-S204 (SEQ ID NO: 2568)  
GFREGQRWYWFVAQVT-NH<sub>2</sub> (SEQ ID NO: 246)  
VASGHVLHGQFYRWFDQFALEE-NH<sub>2</sub> (SEQ ID NO: 2569)  
VGDFCVSHDCFYGWFLRESMQ-NH<sub>2</sub> (SEQ ID NO: 2570)  
DLRVLCELFGGAYVLGYCSE-NH<sub>2</sub> (SEQ ID NO: 2571)  
HLSVGEELSWWVALLGQWAR-NH<sub>2</sub> (SEQ ID NO: 2572)  
APVSTEELRWGALLFGQWAG-NH<sub>2</sub> (SEQ ID NO: 2573)  
ALEEEWAWVQVRSIRSGLPL-NH<sub>2</sub> (SEQ ID NO: 2574)  
WLEHEWAQIQCELYGRGCTY-NH<sub>2</sub> (SEQ ID NO: 2575)

AAVHEQFYDWFADQYEE-NH<sub>2</sub> (SEQ ID NO: 2576)  
QAPSNFYDWFVREWDEE-NH<sub>2</sub> (SEQ ID NO: 2577)  
QSFYDYIEELLGGEWKK-NH<sub>2</sub> (SEQ ID NO: 2578)  
DPFYQGLWEWLRESGEE-NH<sub>2</sub> (SEQ ID NO: 2579)  
(S204)<sub>2-7</sub> (SEQ ID NO: 2580)  
(S204)<sub>2-9</sub> (SEQ ID NO: 2581)  
(S204)<sub>2-12</sub> (SEQ ID NO: 2582)  
(S204)<sub>2-13</sub> (SEQ ID NO: 2583)  
DWLQRNANFYDWFVAEL-Lig (SEQ ID NO: 2584)  
Lig-DWLQRNANFYDWFVAEL (SEQ ID NO: 2585)  
(S209)<sub>2-9</sub> (SEQ ID NO: 2586)  
(S210)<sub>2-9</sub> (SEQ ID NO: 2587)  
LigKHL CVLEELFWGASLFGYCSGK KKK (SEQ ID NO: 2588)  
KHL CVLEELFWGASLFGYCSGK KKK-Lig (SEQ ID NO: 2589)  
(S294)<sub>2-14</sub> (SEQ ID NO: 2590)  
(S295)<sub>2-14</sub> (SEQ ID NO: 2591)  
S-D-G-F-Y-N-A-Acy-E-L-L-S (SEQ ID NO: 2592)  
S-G-P-F-Y-E-E-Acy-E-L-L-W-Aib (SEQ ID NO: 2593)  
G-G-S-F-Y-D-D-Acy-E-Aib-L-W-Aib (SEQ ID NO: 2594)  
N-Aib-P-F-Y-D-E-Acy-D-E-Cha-W-Aib (SEQ ID NO: 2595)  
GRVDWLQRNANFYDWFVAEAcyG-NH<sub>2</sub> (SEQ ID NO: 2596)  
and wherein underlined numbers represent a linker as defined in  
Table 18.

47. An amino acid sequence which specifically binds IR such that binding to IGF-1R is at or below background and wherein said amino acid sequence comprises X<sub>1</sub>X<sub>2</sub>X<sub>3</sub>X<sub>4</sub>X<sub>5</sub> wherein X<sub>1</sub>, X<sub>2</sub>, and X<sub>5</sub> are selected from the group consisting of phenylalanine and tyrosine, X<sub>3</sub> is selected from the group consisting of aspartic acid, glutamic acid, glycine and serine, and X<sub>4</sub> is selected from group consisting of tryptophan, tyrosine and phenylalanine.

48. A method of modulating insulin activity in mammalian cells, said method comprising administering to said cells an amino acid sequence which binds IR and comprises the sequence of amino acids  $X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}$  wherein  $X_6$  and  $X_7$  are aromatic amino acids or glutamine,  $X_8$ ,  $X_9$ ,  $X_{11}$  and  $X_{12}$  may be any amino acid,  $X_{10}$  and  $X_{13}$  are hydrophobic amino acids.
49. The method according to claim 48 wherein  $X_6$  and  $X_7$  are selected from group consisting of phenylalanine and tyrosine, and  $X_{10}$  and  $X_{13}$  are selected from group consisting of leucine, isoleucine, tryptophan, phenylalanine methionine and valine.
50. The method according to claim 48 wherein  $X_6$  is phenylalanine and  $X_7$  is tyrosine.
51. The method according to claim 50 wherein  $X_{10}$  is isoleucine.
52. The method according to claim 50 wherein  $X_{10}$  is leucine.
53. The method according to claim 50 wherein  $X_{13}$  is leucine.
54. The method according to claim 50 wherein  $X_9$  is tyrosine and  $X_{10}$  is phenylalanine.
55. (Once Amended) The method according to claim 50 wherein the amino acid sequence is selected from  $FYX_8X_9LX_{11}X_{12}L$  (SEQ ID NO: 2416),  $FYX_8X_9IX_{11}X_{12}L$  (SEQ ID NO: 2417) and  $FYX_8YFX_{11}X_{12}L$  (SEQ ID NO: 2419).



56. (Once Amended) The method according to claim 55 wherein the amino acid sequence comprises  $FYX_8X_9LX_{11}X_{12}L$  (SEQ ID NO: 2416).
57. (Once Amended) The method according to claim 55 wherein the amino acid sequence comprises  $FYX_8YFX_{11}X_{12}L$  (SEQ ID NO: 2419).
58. The method according to claim 48 wherein the amino acid sequence  $X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}$  further comprises amino acids  $X_{98}$  and  $X_{99}$  at the amino terminal end and  $X_{100}$  at the carboxy terminal end to form  $X_{98}X_{99}X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}X_{100}$  and wherein  $X_{98}$  is optionally aspartic acid and  $X_{99}$  is independently an amino acid selected from the group consisting of glycine, glutamine and proline, and  $X_{100}$  is a hydrophobic amino acid.
59. The method according to claim 58 wherein  $X_{100}$  is an aliphatic amino acid.
60. The method according to claim 59 wherein  $X_{100}$  is leucine.
61. The method according to claim 48 wherein the amino acid sequence binds to the insulin receptor with an affinity of at least about  $10^{-5}$  M.
62. The method according to claim 61 wherein the affinity is between about  $10^{-7}$  M.

63. (Once Amended) The method according to claim 48 wherein the amino acid sequence comprises DYKDFYDAIDQLVRGSARAGGTRD (SEQ ID NO: 2379) or KDRAFYNGLRDLVGAVYGAWD (SEQ ID NO: 2637).
64. The method according to claim 48 wherein the amino acid sequence is selected from the group of amino acid sequences listed in Figures 2A through 2P.
65. An amino acid sequence comprising  $X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}$  wherein  $X_6$  and  $X_7$  are aromatic amino acids or glutamine,  $X_8$ ,  $X_9$ ,  $X_{11}$  and  $X_{12}$  may be any amino acid,  $X_{10}$  and  $X_{13}$  are hydrophobic amino acids and wherein said amino acid sequence binds to IGF-1R.
66. The amino acid sequence according to claim 65 wherein the binding occurs at an affinity ( $K_d$ ) of at least about  $10^{-5}$  M.
67. The amino acid sequence according to claim 66 wherein the binding occurs at an affinity ( $K_d$ ) of at least about  $10^{-7}$  M.
68. The amino acid sequence according to claim 65 wherein  $X_6$  and  $X_7$  are phenylalanine or tyrosine, and  $X_{10}$  and  $X_{13}$  are leucine, isoleucine, tryptophan, phenylalanine or methionine.
69. The amino acid sequence according to claim 68 wherein  $X_6$  is phenylalanine and  $X_7$  is tyrosine.
70. The amino acid sequence according to claim 68 wherein  $X_{10}$  is isoleucine.

71. The amino acid sequence according to claim 68 wherein X<sub>10</sub> is leucine.
72. The amino acid sequence according to claim 69 wherein X<sub>13</sub> is leucine.
73. The amino acid sequence according to claim 69 wherein X<sub>9</sub> is tyrosine and X<sub>10</sub> is phenylalanine.
74. (Once Amended) The amino acid sequence according to claim 68 wherein the amino acid sequence comprises an amino acid sequence selected from FYX<sub>8</sub>X<sub>9</sub>LX<sub>11</sub>X<sub>12</sub>L (SEQ ID NO: 2416), FYX<sub>8</sub>X<sub>9</sub>IX<sub>11</sub>X<sub>12</sub>L (SEQ ID NO: 2417) and FYX<sub>8</sub>YFX<sub>11</sub>X<sub>12</sub>L (SEQ ID NO: 2419).
75. (Once Amended) The amino acid sequence according to claim 74 wherein the amino acid sequence comprises FYX<sub>8</sub>X<sub>9</sub>IX<sub>11</sub>X<sub>12</sub>L (SEQ ID NO: 2416).
76. (Once Amended) The amino acid sequence according to claim 74 wherein the amino acid sequence comprises FYX<sub>8</sub>X<sub>9</sub>LX<sub>11</sub>X<sub>12</sub>L (SEQ ID NO: 2416).
77. (Once Amended) The amino acid sequence according to claim 74 wherein the amino acid sequence is FYX<sub>8</sub>YFX<sub>11</sub>X<sub>12</sub>L (SEQ ID NO: 2419).

78. The amino acid sequence according to claim 65 wherein the amino acid sequence  $X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}$  further comprises amino acids  $X_{98}$  and  $X_{99}$  at the amino terminal end and  $X_{100}$  at the carboxy terminal end to form  $X_{98}X_{99}X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}X_{100}$  and wherein  $X_{98}$  is optionally aspartic acid and  $X_{99}$  is independently an amino acid selected from the group consisting of glycine, glutamine and proline, and  $X_{100}$  is a hydrophobic amino acid.
79. The amino acid sequence according to claim 78 wherein  $X_{100}$  is an aliphatic amino acid.
80. The amino acid sequence according to claim 79 wherein  $X_{100}$  is leucine.
81. (Once Amended) The amino acid sequence according to claim 68 wherein the amino acid sequence comprises  
DYKDFYDAIDQLVRGSARAGGTRD (SEQ ID NO: 2379) or  
KDRAFYNGLRDLVGAVYGAWDKK (SEQ ID NO: 2117).
82. (Once Amended) The sequence according to claim 81 wherein the amino acid sequence comprises DYKDFYDAIDQLVRGSARAGGTRD (SEQ ID NO: 2379).
83. An amino acid sequence comprising an amino acid sequence selected from the group consisting of amino sequences listed in Figures 2A through 2P.
84. (Once Amended) An amino acid sequence comprising a sequence selected from the group consisting of

SFYEAHQLLGV (SEQ ID NO: 1964),  
NSFYALRMLSS (SEQ ID NO: 2638),  
SLNFYDALQLLA (SEQ ID NO: 2639),  
SSNFYQALMLLS (SEQ ID NO: 2471),  
SDGFYNAIELLS (SEQ ID NO: 2460,  
HETFYSMIRSLA (SEQ ID NO: 2640),  
HDPFYMMKSL (SEQ ID NO: 2641) and  
WSDFYSYFQGLD (SEQ ID NO: 2469).

85. (Once Amended) The amino acid sequence according to claim 65 wherein the sequence comprises the amino acid sequence  $X_{115}X_{116}X_{117}X_{118}FYX_8YFX_{11}X_{12}LX_{119}X_{120}X_{121}X_{122}$  (SEQ ID NO: 2420) wherein  $X_{115}$  is selected from the group consisting of tryptophan, glycine, aspartic acid, glutamic acid and arginine,  $X_{116}$  is selected from the group consisting of aspartic acid, histidine, glycine and asparagine,  $X_{117}$  and  $X_{118}$  are selected from the group consisting of glycine, aspartic acid, glutamic acid, asparagine, and alanine,  $X_8$  is selected from the group consisting of arginine, glycine, glutamic acid and serine,  $X_{11}$  is selected from the group consisting of glutamic acid, asparagine, glutamine and tryptophan,  $X_{12}$  is selected from the group consisting of aspartic acid, glutamic acid, glycine, lysine, and glutamine,  $X_{119}$  is selected from the group consisting of glutamic acid, glycine, glutamine, aspartic acid and alanine,  $X_{120}$  is selected from the group consisting of glutamic acid, aspartic acid, glycine and glutamine,  $X_{121}$  is selected from the group consisting of tryptophan, tyrosine, glutamic acid, phenylalanine, histidine and aspartic acid, and  $X_{122}$  is selected from the group consisting of glutamic acid, aspartic acid, and glycine.
86. The amino acid sequence according to claim 85 wherein  $X_{115}$  is tryptophan,  $X_{117}$  is selected from glycine, aspartic acid, glutamic acid and asparagine;  $X_{118}$  is selected from glycine, aspartic acid, glutamic acid and alanine;  $X_{11}$ ,  $X_{119}$ ,  $X_{120}$ , and  $X_{122}$  are glutamic acid;  $X_{12}$  is aspartic acid, and  $X_{121}$  is tryptophan or tyrosine.

87. An amino acid sequence comprising  $X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}$  wherein  $X_6$  and  $X_7$  are aromatic amino acids or glutamine,  $X_8$ ,  $X_9$ ,  $X_{11}$  and  $X_{12}$  may be any amino acid,  $X_{10}$  and  $X_{13}$  are hydrophobic amino acids and wherein said amino acid sequence binds to IR such that binding to IGF-1R is at or below background.
88. A method of binding to Site 1 of IR from mammalian cells, said method comprising contacting IR with an amino acid sequence which binds IR and comprises the sequence of  $X_{14}X_{15}X_{16}X_{17}X_{18}X_{19}X_{20}X_{21}$  wherein  $X_{14}$ ,  $X_{17}$ , and  $X_{18}$  are hydrophobic amino acids,  $X_{15}$ ,  $X_{16}$ , and  $X_{19}$  are any amino acid, and  $X_{20}$  and  $X_{21}$  are aromatic amino acids.
89. The method according to claim 88 wherein  $X_{14}$  and  $X_{17}$  are selected from the group consisting of leucine, isoleucine and valine;  $X_{20}$  is selected from group consisting of tyrosine and histidine; and  $X_{21}$  is selected from group consisting of phenylalanine and tyrosine.
90. The method according to claim 89 wherein  $X_{14}$  and  $X_{17}$  are leucine.
91. The method according to claim 89 wherein  $X_{14}$  is leucine.
92. The method according to claim 89 wherein  $X_{17}$  is leucine.
93. The method according to claim 89 wherein  $X_{20}$  is tyrosine.
94. The method according to claim 89 wherein  $X_{21}$  is phenylalanine.
95. The method according to claim 90 wherein  $X_{15}$  is a large amino acid.

96. The method according to claim 89 wherein said amino acid sequence further comprises an amino acid extension comprising  $X_{101}X_{102}X_{103}$  wherein  $X_{103}$  is bound to  $X_{14}$  at the amino terminus and  $X_{101}$  and  $X_{102}$  are polar amino acids and  $X_{103}$  is a hydrophobic amino acid.
97. The method according to claim 96 wherein  $X_{101}$  and  $X_{102}$  are independently aspartic acid or glutamic acid and  $X_{103}$  is leucine, isoleucine or valine.
98. A method of binding to Site 1 of IGF-1R from mammalian cells, said method comprising contacting IGF-1R with an amino acid sequence which binds IR and comprises the sequence of  $X_{14}X_{15}X_{16}X_{17}X_{18}X_{19}X_{20}X_{21}$  wherein  $X_{14}$ ,  $X_{17}$ , and  $X_{18}$  are hydrophobic amino acids,  $X_{15}$ ,  $X_{16}$ , and  $X_{19}$  are any amino acid, and  $X_{20}$  and  $X_{21}$  are aromatic amino acids.
99. The method according to claim 98 wherein  $X_{14}$  and  $X_{17}$  are selected from the group consisting of leucine, isoleucine and valine;  $X_{18}$  is an aromatic amino acid;  $X_{20}$  is selected from group consisting of tyrosine and histidine; and  $X_{21}$  is selected from group consisting of phenylalanine and tyrosine.
100. The method according to claim 98 wherein the amino acid sequence comprises a sequence selected from the sequences in Figures 3A through 3D.
101. An amino acid sequence which binds Site 1 of IR from mammalian cells, said sequence comprising  $X_{14}X_{15}X_{16}X_{17}X_{18}X_{19}X_{20}X_{21}$  wherein  $X_{14}$ ,  $X_{17}$ , and  $X_{18}$  are hydrophobic amino acids,  $X_{15}$ ,  $X_{16}$ , and  $X_{19}$  are any amino acid, and  $X_{20}$  and  $X_{21}$  are aromatic amino acids.

102. The amino acid sequence according to claim 101 wherein  $X_{14}$  and  $X_{17}$  are selected from the group consisting of leucine, isoleucine and valine;  $X_{20}$  is selected from group consisting of phenylalanine and tyrosine.
103. The amino acid sequence according to claim 102 wherein  $X_{14}$  and  $X_{17}$  are leucine.
104. The amino acid sequence according to claim 102 wherein  $X_{14}$  is leucine.
105. The amino acid sequence according to claim 102 wherein  $X_{17}$  is leucine.
106. The amino acid sequence according to claim 102 wherein amino acid  $X_{18}$  is tryptophan.
107. The amino acid sequence according to claim 103 wherein  $X_{20}$  is tyrosine.
108. The amino acid sequence according to claim 107 wherein  $X_{21}$  is phenylalanine.
109. The amino acid sequence according to claim 103 wherein  $X_{15}$  is a large amino acid.
110. The amino acid sequence according to claim 101 wherein at least one amino acid is a D-amino acid.



111. The amino acid sequence according to claim 65 wherein at least one amino acid is a D-amino acid.
112. The amino acid sequence according to claim 102 wherein said amino acid sequence further comprises an amino acid extension comprising  $X_{101}X_{102}X_{103}$  wherein  $X_{103}$  is bound to  $X_{14}$  at the amino terminus and  $X_{101}$  and  $X_{102}$  are polar amino acids and  $X_{103}$  is a hydrophobic amino acid.
113. The amino acid sequence according to claim 112 wherein  $X_{101}$  and  $X_{102}$  are independently aspartic acid or glutamic acid and  $X_{103}$  is leucine, isoleucine or valine.
114. An amino acid sequence which binds Site 1 of IGF-1R from mammalian cells such that binding to IR is at or below background, said sequence comprising  $X_{14}X_{15}X_{16}X_{17}X_{18}X_{19}X_{20}X_{21}$  wherein  $X_{14}$ ,  $X_{17}$ , and  $X_{18}$  are hydrophobic amino acids,  $X_{15}$ ,  $X_{16}$ , and  $X_{19}$  are any amino acid, and  $X_{20}$  and  $X_{21}$  are aromatic amino acids.
115. The amino acid sequence according to claim 114 wherein  $X_{14}$  and  $X_{17}$  are selected from the group consisting of leucine, isoleucine and valine;  $X_{18}$  is an aromatic amino acid;  $X_{20}$  is selected from group consisting of tyrosine and histidine; and  $X_{21}$  is selected from group consisting of phenylalanine and tyrosine.

116. A method of binding to Site 2 of IR from mammalian cells, said method comprising contacting said cells with an amino acid sequence comprising  
 $X_{22}X_{23}X_{24}X_{25}X_{26}X_{27}X_{28}X_{29}X_{30}X_{31}X_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}X_{40}X_{41}$   
wherein  $X_{22}$ ,  $X_{25}$ ,  $X_{26}$ ,  $X_{28}$ ,  $X_{29}$ ,  $X_{30}$ ,  $X_{33}$ ,  $X_{34}$ ,  $X_{35}$ ,  $X_{37}$ ,  $X_{38}$ ,  $X_{40}$  and  $X_{41}$  are any amino acid;  $X_{23}$  is any hydrophobic amino acid;  $X_{27}$  is a polar amino acid;  $X_{31}$  is an aromatic amino acid;  $X_{32}$  is a small amino acid; and wherein at least one cysteine is located at positions  $X_{24}$  through  $X_{27}$  and one at  $X_{39}$  or  $X_{40}$ .
117. The method according to claim 116 wherein  $X_{24}$  and  $X_{39}$  are cysteines.
118. The method according to claim 117 wherein  $X_{23}$  is selected from leucine, isoleucine, methionine and valine;  $X_{27}$  is selected from glutamic acid, aspartic acid, asparagine, and glutamine;  $X_{31}$  is tryptophan,  $X_{32}$  is glycine; and  $X_{36}$  is any aromatic amino acid.
119. The method according to claim 118 wherein the binding to IR occurs at an affinity ( $K_d$ ) of at least about  $10^{-5}$  M.
120. The method according to claim 116 wherein  $X_{23}$  is leucine,  $X_{27}$  is glutamic acid,  $X_{31}$  is tryptophan, and  $X_{32}$  is glycine.
121. (Once Amended) The method according to claim 116 wherein the amino acid sequence is HLCVLEELFWGASLFGYCSG (SEQ ID NO: 1509).

122. An amino acid sequence which binds IR, said amino acid sequence comprising  
 $X_{22}X_{23}X_{24}X_{25}X_{26}X_{27}X_{28}X_{29}X_{30}X_{31}X_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}X_{40}X_{41}$   
wherein  $X_{22}$ ,  $X_{25}$ ,  $X_{26}$ ,  $X_{28}$ ,  $X_{29}$ ,  $X_{30}$ ,  $X_{33}$ ,  $X_{34}$ ,  $X_{35}$ ,  $X_{37}$ ,  $X_{38}$ ,  $X_{40}$  and  $X_{41}$   
are any amino acid,  $X_{23}$  is any hydrophobic amino acid,  $X_{27}$  is a polar  
amino acid;  $X_{31}$  is an aromatic amino acid;  $X_{32}$  is a small amino acid,  
and wherein at least one cysteine is located at positions  $X_{24}$  through  
 $X_{27}$  and one at  $X_{39}$  or  $X_{40}$ .
123. The amino acid sequence according to claim 122 wherein  $X_{24}$  and  $X_{39}$   
are cysteines.
124. The amino acid sequence according to claim 123 wherein  $X_{23}$  is  
selected from methionine, valine, and leucine;  $X_{27}$  is selected from  
glutamic acid, alanine, glycine, glutamine, aspartic acid and valine;  
 $X_{31}$  and  $X_{32}$  are small amino acids; and  $X_{36}$  is an aromatic amino acid.
125. The amino acid sequence according to claim 122 wherein the binding  
to IR occurs at an affinity ( $K_d$ ) of at least about  $10^{-5}$  M.
126. The amino acid sequence according to claim 124 wherein  $X_{23}$  is  
leucine,  $X_{27}$  is glutamic acid,  $X_{31}$  is tryptophan, and  $X_{32}$  is glycine.
127. (Once Amended) The amino acid sequence according to claim 122  
wherein the amino acid sequence is HLCVLEELFWGASLFGYCSG  
(SEQ ID NO: 1509).

128. A method of modulating insulin activity in mammalian cells, said method comprising administering to said cells an amino acid sequence which binds IR and comprises the sequence  $X_{42} X_{43} X_{44} X_{45} X_{46} X_{47} X_{48} X_{49} X_{50} X_{51} X_{52} X_{53} X_{54} X_{55} X_{56} X_{57} X_{58} X_{59} X_{60} X_{61}$  wherein  $X_{42}$ ,  $X_{43}$ ,  $X_{44}$ ,  $X_{45}$ ,  $X_{53}$ ,  $X_{55}$ ,  $X_{56}$ ,  $X_{58}$ ,  $X_{60}$  and  $X_{61}$  are any amino acid;  $X_{43}$ ,  $X_{46}$ ,  $X_{49}$ ,  $X_{50}$  and  $X_{54}$  are hydrophobic amino acids;  $X_{47}$  and  $X_{59}$  are cysteines;  $X_{48}$  is a polar amino acid;  $X_{51}$ ,  $X_{52}$  and  $X_{57}$  are small amino acids.
129. The method according to claim 128 wherein  $X_{43}$  and  $X_{46}$  are leucine;  $X_{48}$  is selected from the group consisting of aspartic acid and glutamic acid;  $X_{50}$  is phenylalanine or tyrosine; and  $X_{51}$ ,  $X_{52}$  and  $X_{57}$  are glycine.
130. The method according to claim 129 wherein  $X_{48}$  is glutamic acid and  $X_{50}$  is a phenylalanine.
131. (Once Amended) The method according to claim 130 wherein the amino acid sequence is  $X_{42} X_{43} X_{44} X_{45} \text{LCE} X_{49} \text{FGG} X_{53} X_{54} X_{55} X_{56} \text{GX}_{58} \text{C} X_{60} X_{61}$  (SEQ ID NO: 2422).
132. (Once Amended) The method according the claim 131 wherein the amino acid sequence comprises DLRVLCSELFGGAYVLGYCSE (SEQ ID NO: 1732) or DLRVLCSELFGGAYVRGYCSE (SEQ ID NO: 2642).
133. The method according to claim 128 wherein the binding to IR occurs at an affinity ( $K_d$ ) of at least about  $10^{-5}$  M.

134. An amino acid sequence which binds IR, said amino acid sequence comprising X<sub>42</sub> X<sub>43</sub> X<sub>44</sub> X<sub>45</sub> X<sub>46</sub> X<sub>47</sub> X<sub>48</sub> X<sub>49</sub> X<sub>50</sub> X<sub>51</sub> X<sub>52</sub> X<sub>53</sub> X<sub>54</sub> X<sub>55</sub> X<sub>56</sub>X<sub>57</sub>X<sub>58</sub>X<sub>59</sub> X<sub>60</sub> X<sub>61</sub> wherein X<sub>42</sub>, X<sub>43</sub>, X<sub>44</sub>, X<sub>45</sub>, X<sub>53</sub>, X<sub>55</sub>, X<sub>60</sub> and X<sub>61</sub> are any amino acid; X<sub>43</sub>, X<sub>46</sub>, X<sub>49</sub>, X<sub>50</sub> and X<sub>54</sub> are hydrophobic amino acids; X<sub>47</sub> and X<sub>59</sub> are cysteines; X<sub>48</sub> is a polar amino acid; and X<sub>51</sub>, X<sub>52</sub> and X<sub>57</sub> are small amino acids.
135. The amino acid sequence according to claim 134 wherein X<sub>43</sub> and X<sub>46</sub> are leucine; X<sub>48</sub> is selected from the group consisting of aspartic acid and glutamic acid; X<sub>50</sub> is phenylalanine or tyrosine; and X<sub>51</sub>, X<sub>52</sub> and X<sub>57</sub> are glycine.
136. The amino acid sequence according to claim 135 wherein X<sub>48</sub> is glutamic acid and X<sub>50</sub> is phenylalanine.
137. (Once Amended) The amino acid sequence according to claim 136 wherein the amino acid sequence comprises X<sub>43</sub> X<sub>44</sub> X<sub>45</sub> LCE X<sub>49</sub> FGG X<sub>53</sub> X<sub>54</sub> X<sub>55</sub> X<sub>56</sub> G X<sub>58</sub> C X<sub>60</sub> X<sub>61</sub> (SEQ ID NO: 2422).
138. (Once Amended) The amino acid sequence according to claim 137 wherein an amino acid sequence comprises DLRVLCELFGGAYVLGYCSE (SEQ ID NO: 1732) or DLRVLCELFGGAYVRGYCSE (SEQ ID NO: 2642).

139. A method of modulating insulin activity in mammalian cells, said method comprising administering to said cells an amino acid sequence comprising  $X_{62} X_{63} X_{64} X_{65} X_{66} X_{67} X_{68} X_{69} X_{70} X_{71} X_{72} X_{73} X_{74} X_{75} X_{76} X_{77} X_{78} X_{79} X_{80} X_{81}$  wherein  $X_{62}$ ,  $X_{65}$ ,  $X_{66}$ ,  $X_{68}$ ,  $X_{69}$ ,  $X_{71}$ ,  $X_{73}$ ,  $X_{76}$ ,  $X_{77}$ ,  $X_{78}$ ,  $X_{80}$  and  $X_{81}$  are any amino acid;  $X_{63}$ ,  $X_{70}$ , and  $X_{74}$  are hydrophobic amino acids;  $X_{64}$  is a polar amino acid;  $X_{67}$  and  $X_{75}$  are aromatic amino acids; and  $X_{72}$  and  $X_{79}$  are cysteines.
140. The method according to claim 139 wherein  $X_{63}$  is selected from the group consisting of leucine, isoleucine, methionine and valine;  $X_{70}$  and  $X_{74}$  are selected from group consisting of valine, isoleucine, leucine and methionine;  $X_{64}$  is selected from group consisting of aspartic acid and glutamic acid;  $X_{67}$  is tryptophan; and  $X_{75}$  is selected from group consisting of tyrosine and tryptophan.
141. The method according to claim 140 wherein  $X_{66}$  is glutamic acid.
142. The method according to claim 141 wherein  $X_{63}$  is leucine.
143. The method according to claim 140 wherein  $X_{74}$  is valine.
144. The method according to claim 141 wherein  $X_{64}$  is a glutamic acid.
145. The method according to claim 141 wherein  $X_{75}$  is a tyrosine.
146. (Once Amended) The method accord to claim 140 wherein the amino acid sequence comprises WLDQEWA~~WW~~QCEVYGRGCPS (SEQ ID NO: 1735).

147. An amino acid sequence which binds IR, said amino acid sequence comprising  $X_{62}$   $X_{63}$   $X_{64}$   $X_{65}$   $X_{66}$   $X_{67}$   $X_{68}$   $X_{69}$   $X_{70}$   $X_{71}$   $X_{72}$   $X_{73}$   $X_{74}$   $X_{75}$   $X_{76}$   $X_{77}$   $X_{78}$   $X_{79}$   $X_{80}$   $X_{81}$  wherein  $X_{62}$ ,  $X_{65}$ ,  $X_{66}$   $X_{68}$ ,  $X_{69}$ ,  $X_{71}$ ,  $X_{73}$ ,  $X_{76}$ ,  $X_{77}$ ,  $X_{78}$ ,  $X_{80}$  and  $X_{81}$  are any amino acid;  $X_{63}$ ,  $X_{70}$ , and  $X_{74}$  are hydrophobic amino acids;  $X_{64}$  is a polar amino acid;  $X_{67}$  and  $X_{75}$  are aromatic amino acids; and  $X_{72}$  and  $X_{79}$  are cysteines.
148. The amino acid sequence according to claim 147 wherein  $X_{63}$  is selected from the group consisting of leucine, isoleucine, methionine and valine;  $X_{70}$  and  $X_{74}$  are selected from group consisting of valine, isoleucine, leucine and methionine;  $X_{64}$  is selected from group consisting of aspartic acid and glutamic acid;  $X_{67}$  is tryptophan; and  $X_{75}$  is selected from group consisting of tyrosine and tryptophan.
149. The amino acid sequence according to claim 148 wherein  $X_{66}$  is glutamic acid.
150. The amino acid sequence according to claim 149 wherein  $X_{63}$  is leucine.
151. The amino acid sequence according to claim 148 wherein  $X_{74}$  is valine.
152. The amino acid sequence according to claim 149 wherein  $X_{64}$  is glutamic acid.
153. The amino acid sequence according to claim 148 wherein  $X_{75}$  is a tyrosine.

154. (Once Amended) The amino acid sequence accord to claim 148 wherein the amino acid sequence comprises  
WLDQEWAWVQCEVYGRGCPS (SEQ ID NO: 1735).
155. The amino acid sequence according to claim 148 wherein the affinity ( $K_d$ ) of binding to IR is at least  $10^{-5}$  M.
156. The amino acid sequence according to claim 148 wherein the amino acid sequence comprises a sequence selected from the sequences of Figures 6A-6F.
157. A method of modulating insulin activity in mammalian cells, said method comprising administering to said cells an amino acid sequence which binds IR and comprises  
HX<sub>82</sub>X<sub>83</sub>X<sub>84</sub>X<sub>85</sub>X<sub>86</sub>X<sub>87</sub>X<sub>88</sub>X<sub>89</sub>X<sub>90</sub>X<sub>91</sub>X<sub>92</sub> herein X<sub>82</sub> is proline or alanine; X<sub>83</sub> is a small amino acid; X<sub>84</sub> is selected from the group consisting of leucine, serine and threonine; X<sub>85</sub> is a polar amino acid; X<sub>86</sub> is any amino acid; X<sub>87</sub> is an aliphatic amino acid; X<sub>88</sub>, X<sub>89</sub>, X<sub>90</sub> is any amino acid; and X<sub>91</sub> and X<sub>92</sub> are aliphatic amino acids.
158. The method according to claim 157 wherein X<sub>82</sub> is proline; X<sub>83</sub> is selected from the group consisting of proline, serine and threonine; X<sub>84</sub> is leucine; X<sub>85</sub> is selected from the group consisting of glutamic acid, serine, lysine and asparagine; X<sub>86</sub> is a polar amino acid; X<sub>87</sub> is selected from the group consisting of leucine, methionine and isoleucine; and X<sub>91</sub> and X<sub>92</sub> are leucines.
159. The method according to claim 158 wherein X<sub>83</sub> is proline.
160. The method according to claim 158 wherein X<sub>85</sub> is serine.



161. The method according to claim 158 wherein  $X_{86}$  is selected from the group consisting of histidine, glutamic acid, aspartic acid and glutamine.
162. The method according to claim 158 wherein  $X_{87}$  is leucine.
163. The method according to claim 158 wherein  $X_{92}$  is phenylalanine.
164. (Once Amended) The method according to claim 160 wherein the amino acid sequence is HPPLSX<sub>86</sub> LX<sub>88</sub> X<sub>89</sub> X<sub>90</sub> LL (SEQ ID NO: 2424).
165. (Once Amended) The method according to claim 158 wherein the amino acid sequence is selected from the group consisting of HPPLEHLKAFLL (SEQ ID NO: 1869), HPPLSELKLFLI (SEQ ID NO: 2643), HPSLSDMRWILL (SEQ ID NO: 2644), HPTSKEIYAKLL (SEQ ID NO: 2645), HPTSKEIYAKLL (SEQ ID NO: 2645), HPSTNQMLMKLF (SEQ ID NO: 2646) and HAPLSVLQALL (SEQ ID NO: 2647).
166. An amino acid sequence which binds IR, said amino acid sequence comprising HX<sub>82</sub>X<sub>83</sub>X<sub>84</sub>X<sub>85</sub>X<sub>86</sub>X<sub>87</sub>X<sub>88</sub>X<sub>89</sub>X<sub>90</sub>X<sub>91</sub>X<sub>92</sub> herein  $X_{82}$  is proline or alanine;  $X_{83}$  is a small amino acid;  $X_{84}$  is selected from the group consisting of leucine, serine and threonine;  $X_{85}$  is a polar amino acid;  $X_{86}$  is any amino acid;  $X_{87}$  is an aliphatic amino acid;  $X_{88}$ ,  $X_{89}$ ,  $X_{90}$  is any amino acid; and  $X_{91}$  and  $X_{92}$  are aliphatic amino acids.

167. The amino acid sequence according to claim 166 wherein X<sub>82</sub> is proline; X<sub>83</sub> is selected from the group consisting of proline, serine and threonine; X<sub>84</sub> is leucine; X<sub>85</sub> is selected from the group consisting of glutamic acid, serine, lysine and asparagine; X<sub>86</sub> is a polar amino acid; X<sub>87</sub> is selected from the group consisting of leucine, methionine and isoleucine; and X<sub>91</sub> and X<sub>92</sub> are leucines.
168. The amino acid sequence according to claim 167 wherein X<sub>83</sub> is proline.
169. The amino acid sequence according to claim 167 wherein X<sub>85</sub> is serine.
170. The amino acid sequence according to claim 167 wherein X<sub>86</sub> is selected from the group consisting of histidine, glutamic acid, aspartic acid and glutamine.
171. The amino acid sequence according to claim 167 wherein X<sub>87</sub> is leucine.
172. The amino acid sequence according to claim 167 wherein X<sub>92</sub> is phenylalanine.
173. (Once Amended) The amino acid sequence according to claim 169 wherein the amino acid sequence is HPPLSX<sub>86</sub> LX<sub>88</sub> X<sub>89</sub> X<sub>90</sub> LL (SEQ ID NO: 2424).

174. (Once Amended) The amino acid sequence according to claim 167 wherein the amino acid sequence is selected from the group consisting of HPPLEHLKAFL (SEQ ID NO: 1869), HPPLSELKLFLI (SEQ ID NO: 2643), HPSLSDMRWILL (SEQ ID NO: 2644), HPTSKEIYAKLL (SEQ ID NO: 2645), HPTSKEIYAKLL (SEQ ID NO: 2645), HPSTNQMLMKLF (SEQ ID NO: 2646) and HAPLSVLQALL (SEQ ID NO: 2647).
175. A method modulating insulin activity in mammalian cells, said method comprising administering to said cells an amino acid sequence comprising an amino acid sequence of  $X_{104}X_{105}X_{106}X_{107}X_{108}X_{109}X_{110}X_{111}X_{112}X_{113}X_{114}$  wherein at least one of the amino acids of  $X_{106}$  through  $X_{111}$  are tryptophan; wherein  $X_{104}$  and  $X_{114}$  are both small amino acids; wherein  $X_{105}$  is any amino acid; and wherein at least one of  $X_{104}$ ,  $X_{105}$ ,  $X_{106}$  and one of  $X_{112}$   $X_{113}$   $X_{114}$  are cysteine residues.
176. The method according to claim 175 wherein at least two of the amino acids of  $X_{106}$  through  $X_{111}$  are tryptophan which are separated from each other by at least two amino acids.
177. The method according to claim 176 wherein the separating amino acids are selected from the group consisting of proline, threonine and tyrosine.
178. (Once Amended) The method according to claim 177 wherein the amino acid sequence comprises WPTYW (SEQ ID NO: 2425).
179. The method according to claim 178 wherein  $X_{105}$  and  $X_{113}$  are cysteine residues.

180. The method according to claim 178 wherein  $X_{104}$  and  $X_{114}$  are selected from the group consisting of alanine and glycine.
181. The method according to claim 180 wherein  $X_{104}$  is alanine and  $X_{114}$  is glycine.
182. The method according to claim 181 wherein  $X_{105}$  is valine.
183. The method according to claim 182 wherein  $X_{112}$  is asparagine.
184. The method according to claim 198 wherein the affinity ( $K_d$ ) of binding to IR is at least about  $10^{-5}$  M.
185. A method of modulating insulin activity in mammalian cells, said method comprising administering to said cells an amino acid sequence comprising an amino acid sequence selected from the group listed in Figure 8.
186. (Once Amended) The method according to claim 185 wherein the sequence comprises ACVWPTYWNCG (SEQ ID NO: 1874).
187. An amino acid sequence which binds and IR and comprising an amino acid sequence of  $X_{104}X_{105}X_{106}X_{107}X_{108}X_{109}X_{110}X_{111}X_{112}X_{113}X_{114}$  wherein at least one of the amino acids of  $X_{106}$  through  $X_{111}$  are tryptophan; wherein  $X_{104}$  and  $X_{114}$  are both small amino acids; wherein  $X_{105}$  is any amino acid; and wherein at least one of  $X_{104}$ ,  $X_{105}$ ,  $X_{106}$  and one of  $X_{112}$   $X_{113}$   $X_{114}$  are cysteine residues.

188. The amino acid sequence according to claim 187 wherein at least two of the amino acids of  $X_{106}$  through  $X_{111}$  are tryptophan which are separated from each other by at least two amino acids.
189. The amino acid sequence according to claim 188 wherein the separating amino acids are selected from the group consisting of proline, threonine and tyrosine.
190. (Once Amended) The amino acid sequence according to claim 189 wherein the amino acid sequence comprises WPTYW (SEQ ID NO: 2425).
191. The amino acid sequence according to claim 190 wherein  $X_{105}$  and  $X_{113}$  are cysteine residues.
192. The amino acid sequence according to claim 190 wherein  $X_{104}$  and  $X_{114}$  are selected from the group consisting of alanine and glycine.
193. The amino acid sequence according to claim 190 wherein  $X_{104}$  is alanine and  $X_{114}$  is glycine.
194. The amino acid sequence according to claim 193 wherein  $X_{105}$  is valine.
195. The amino acid sequence according to claim 194 wherein  $X_{112}$  is asparagine.
196. The amino acid sequence according to claim 202 wherein the affinity ( $K_d$ ) of binding to IR is at least about  $10^{-5}$  M.

197. An amino acid sequence which binds IR from mammalian cells comprising an amino acid sequence selected from the group listed in Figure 8.
198. (Once Amended) The amino acid sequence according to claim 197 comprising ACVWPTYWNCG (SEQ ID NO: 1874).
199. (Once Amended) A method of providing insulin agonist activity to mammalian cells, said method comprising administering to said cells an amino acid sequence comprising DYKDLCSWGVIRIGWLAGLCPKK (SEQ ID NO: 2152).
200. A method of modulating insulin activity in mammalian cells, said method comprising administering to said cells an amino acid sequence comprising an amino acid sequence selected from the group listed in Figures 9 through 11.
201. (Once Amended) An amino acid sequence comprising DYKDLCSWGVIRIGWLAGLCPKK (SEQ ID NO: 2152).
202. An amino acid sequence comprising an amino acid sequence selected from the group listed in Figures 9 through 11.
203. An amino acid sequence comprising at least two amino acid sequences which independently bind IR, with the proviso that at least one of the sequences is not insulin or a fragment thereof.
204. The amino acid sequence according to claim 203 wherein the two amino acid sequences bind to Site 1 of IR.

205. The amino acid sequence according to claim 203 wherein one amino acid sequence binds to Site 1, and the other binds to Site 2 of IR.
206. The amino acid sequence according to claim 203, wherein at least one of the sequences is selected from the group consisting of  $X_1X_2X_3X_4X_5$  wherein  $X_1$ ,  $X_2$ ,  $X_4$ , and  $X_5$  are aromatic amino acids, and  $X_3$  may be any polar amino acid;  $X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}$  wherein  $X_6$  and  $X_7$  are aromatic amino acids or glutamine,  $X_8$ ,  $X_9$ ,  $X_{11}$  and  $X_{12}$  may be any amino acid,  $X_{10}$  and  $X_{13}$  are hydrophobic amino acids; and  $X_{14}X_{15}X_{16}X_{17}X_{18}X_{19}X_{20}X_{21}$  wherein  $X_{14}$ ,  $X_{17}$ , and  $X_{18}$  are hydrophobic amino acids,  $X_{15}$ ,  $X_{16}$ , and  $X_{19}$  are any amino acid, and  $X_{20}$  and  $X_{21}$  are aromatic amino acids.
207. The amino acid sequence according to claim 206, wherein at least one of the sequences is  $X_1X_2X_3X_4X_5$  wherein  $X_1$ ,  $X_2$ ,  $X_4$ , and  $X_5$  are aromatic amino acids, and  $X_3$  may be any polar amino acid.
208. (Once Amended) The amino acid sequence according to claim 206 wherein at least one of the sequences comprises  $FYX_3WF$  (SEQ ID NO: 2415).
209. The amino acid sequence according to claim 206, wherein at least one of the sequences comprises  $X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}$  wherein  $X_6$  and  $X_7$  are aromatic amino acids or glutamine,  $X_8$ ,  $X_9$ ,  $X_{11}$  and  $X_{12}$  may be any amino acid,  $X_{10}$  and  $X_{13}$  are hydrophobic amino acids.
210. (Once Amended) The amino acid sequence according to claim 209, wherein at least one of the sequences comprises  $FYX_8X_9LX_{11}X_{12}L$  (SEQ ID NO: 2416).

211. The amino acid sequence according to claim 206, wherein at least one of the sequences comprises  $X_{14}X_{15}X_{16}X_{17}X_{18}X_{19}X_{20}X_{21}$  wherein  $X_{14}$ ,  $X_{17}$ , and  $X_{18}$  are hydrophobic amino acids,  $X_{15}$ ,  $X_{16}$ , and  $X_{19}$  are any amino acid, and  $X_{20}$  and  $X_{21}$  are aromatic amino acids.
212. (Once Amended) The amino acid sequence according to claim 211 wherein at least one of the sequences comprises  $LX_{15}$ ,  $X_{16}$ ,  $LLX_{19}YF$  (SEQ ID NO: 2648).
213. The amino acid sequence according to claim 203 wherein at least one of the sequences comprises  $X_{22}X_{23}X_{24}X_{25}X_{26}X_{27}X_{28}X_{29}X_{30}X_{31}X_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}X_{40}X_{41}$  wherein  $X_{22}$ ,  $X_{25}$ ,  $X_{26}$ ,  $X_{28}$ ,  $X_{29}$ ,  $X_{30}$ ,  $X_{33}$ ,  $X_{34}$ ,  $X_{35}$ ,  $X_{36}$ ,  $X_{37}$ ,  $X_{38}$ ,  $X_{40}$ , and  $X_{41}$  are any amino acid,  $X_{23}$  is any hydrophobic amino acid;  $X_{27}$  is a polar amino acid;  $X_{31}$  is an aromatic amino acid;  $X_{32}$  is a small amino acid, and wherein at least one cysteine is located at positions  $X_{24}$  through  $X_{27}$  and one at  $X_{39}$  or  $X_{40}$ ;  $X_{42}X_{43}X_{44}X_{45}X_{46}X_{47}X_{48}X_{49}X_{50}X_{51}X_{52}X_{53}X_{54}X_{55}X_{56}X_{57}X_{58}X_{59}X_{60}X_{61}$  wherein  $X_{42}$ ,  $X_{43}$ ,  $X_{44}$ ,  $X_{45}$ ,  $X_{53}$ ,  $X_{55}$ ,  $X_{56}$ ,  $X_{58}$ ,  $X_{60}$  and  $X_{61}$  are any amino acid;  $X_{43}$ ,  $X_{46}$ ,  $X_{49}$ ,  $X_{50}$  and  $X_{54}$  are hydrophobic amino acids;  $X_{47}$  and  $X_{59}$  are cysteine;  $X_{48}$  is a polar amino acid; and  $X_{51}$ ,  $X_{52}$  and  $X_{57}$  are small amino acids; or  $X_{62}X_{63}X_{64}X_{65}X_{66}X_{67}X_{68}X_{69}X_{70}X_{71}X_{72}X_{73}X_{74}X_{75}X_{76}X_{77}X_{78}X_{79}X_{80}X_{81}$  wherein  $X_{62}$ ,  $X_{65}$ ,  $X_{66}$ ,  $X_{68}$ ,  $X_{69}$ ,  $X_{71}$ ,  $X_{73}$ ,  $X_{76}$ ,  $X_{77}$ ,  $X_{78}$ ,  $X_{80}$  and  $X_{81}$  are any amino acid;  $X_{63}$ ,  $X_{70}$ , and  $X_{74}$  are hydrophobic amino acids;  $X_{64}$  is a polar amino acid;  $X_{67}$  and  $X_{75}$  are aromatic amino acids; and  $X_{72}$  and  $X_{79}$  are cysteines.



214. The amino acid sequence according to claim 203 wherein at least one of the sequences comprises  $HX_{82}X_{83}X_{84}X_{85}X_{86}X_{87}X_{88}X_{89}X_{90}X_{91}X_{92}$  herein  $X_{82}$  is proline or alanine;  $X_{83}$  is a small amino acid;  $X_{84}$  is selected from the group consisting of leucine, serine and threonine;  $X_{85}$  is a polar amino acid;  $X_{86}$  is any amino acid;  $X_{87}$  is an aliphatic amino acid;  $X_{88}$ ,  $X_{89}$ ,  $X_{90}$  is any amino acid; and  $X_{91}$  and  $X_{92}$  are aliphatic amino acids or  $X_{104}X_{105}X_{106}X_{107}X_{108}X_{109}X_{110}X_{111}X_{112}X_{113}X_{114}$  wherein at least one of the amino acids of  $X_{106}$  through  $X_{111}$  are tryptophan; wherein  $X_{104}$  and  $X_{114}$  are both small amino acids; wherein  $X_{105}$  is any amino acid; and wherein at least one of  $X_{104}$ ,  $X_{105}$ ,  $X_{106}$  and one of  $X_{112}$   $X_{113}$   $X_{114}$  are cysteine residues.
215. The amino acid sequence according to claim 203 wherein the two amino acid sequences are connected by a peptide or non-peptide linker.
216. The amino acid sequence according to claim 215 wherein the linker is a peptide consisting of about 2 to about 16 amino acids.
217. The amino acid sequence according to claim 215 wherein the linker is a non-peptide.
218. The amino acid sequence according to claim 217 wherein the linker is dialdehyde.
219. (Once Amended) The amino acid sequence according to claim 203 wherein the amino acid sequence is selected from the group consisting of

DYKDDDDKFHENFYDWFVRQVSGSGSGLDALDRLMRYGEERPSL  
AAAGAP (SEQ ID NO: 2649),

DYKDDDDKFHENFYDWFVRQVSGGSHLCVLEELFWGASLFGYCS  
GAAAGAPVPYPDPLEPRAA (SEQ ID NO: 2619),

DYKDDDDKFHENFYDWFVRQVSGGSGGSGGSHLCVLEELFWGAS  
LFGYCSGAAAGAPVPYPDPLEPRAA (SEQ ID NO: 2620),

DYKDDDDKFHENFYDWFVRQVSGGSGGSGGSGGSHLCVLEELF  
WGASLFGYCSGAAAGAPVPYPDPLEPRAA (SEQ ID NO: 2621),

AQPAMAFHENFYDWFVRQVSGGSFHENFYDWFVRQVSAAAGAPV  
PYPDPLEPRAA (SEQ ID NO: 2627),

AQPAMAFHENFYDWFVRQVSGGSFHENFYDWFVRQVSGGSFHE  
NFYDWFVRQVSAAAGAPVPYPDPLEPRAA (SEQ ID NO: 2628),

AQPAMAFHENFYDWFVRQVSGGSGGSGSFHENFYDWFVRQVSAAA  
GAPVPYPDPLEPRAA (SEQ ID NO: 2629),

AQPAMAFHENFYDWFVRQVSGGSGGSGGSGSFHENFYDWFVRQVS  
AAAGAPVPYPDPLEPRAA (SEQ ID NO: 2630) and

AQPAMAFHENFYDWFVRQVSGGSGGSGGSGGSGSFHENFYDWFVR  
QVSAAAGAPVPYPDPLEPRAA (SEQ ID NO: 2631).

220. A nucleic acid sequence encoding amino acid sequence which binds to IR at Site 1 and/or Site 2, with the proviso that the sequence is not insulin, IGF, or fragments thereof.
221. (Once Amended) The nucleic acid sequence according to claim 220 wherein the nucleic acid sequence encodes for an amino acid sequence selected from the group consisting of FYDWF (SEQ ID NO: 2411), FYEWF (SEQ ID NO: 2412), FHENFYDWF (SEQ ID NO: 2635), FHENFYDWFVRQVSK (SEQ ID NO: 2115), DYKDVTFTSAVFHENFYDWFVRQVSKK (SEQ ID NO: 2111), GRVDWLQRNANFYDWFVAELG (SEQ ID NO: 2163) and APTFYAWFNQQT (SEQ ID NO: 1870).
222. (Once Amended) The nucleic acid sequence according to claim 220 wherein the nucleic acid sequence encodes for an amino acid sequence selected from the group consisting of DYKDFYDAIDQLVRGSARAGGTRDKK (SEQ ID NO: 2116) and KDRAFYNGLRDLVGAVYGAWDKK (SEQ ID NO: 2117).
223. (Once Amended) The nucleic acid sequence according to claim 220 wherein the nucleic acid sequence encodes for an amino acid sequence selected from the group consisting of SFYEAIHQLLGV (SEQ ID NO: 1964),  
NSFYEALRMLSS (SEQ ID NO: 2638),  
SLNFYDALQLLA (SEQ ID NO: 2639),  
SSNFYQALMLLS (SEQ ID NO: 2471),  
SDGFYNAIELLS (SEQ ID NO: 2460),  
HETFYSMIRSLA (SEQ ID NO: 2640),  
HDPFYSMMKSL (SEQ ID NO: 2641) and  
WSDFYSYFQGL (SEQ ID NO: 2650).

224. A kit for identifying a compound which binds IGF-1 receptor, comprising a IGF-1 receptor and an amino acid sequence selected from Formulas 1-10, or the amino acid sequences of Figures 9-11, which bind to the receptor at Site 1 or Site 2.
225. (Once Amended) The kit according to claim 224, wherein the amino acid sequence comprises the amino acid sequence FYDWF (SEQ ID NO: 2411).
226. (Once Amended) The kit according to claim 225, wherein the amino acid sequence comprises the amino acid sequence SAKNFYDWFVKK (SEQ ID NO: 2112).
227. (Once Amended) The kit according to claim 226 wherein the amino acid sequence comprises the amino acid sequence FYSLLASL (SEQ ID NO: 2651).
228. (Once Amended) The kit according to claim 227 wherein the amino acid sequence comprises the amino acid sequence QMKDIFYSLLASLAAKK (SEQ ID NO: 2652).
229. A kit for identifying a compound which binds IR comprising IR and an amino acid sequence selected from Formulas 1-10 or the amino acid sequences of Figures 9 and 11 which bind IR at Site 1 or Site 2.
230. A pharmaceutical composition comprising a amino acid sequence which binds specifically to IGF-1 receptor at Site 1 and is an IGF agonist, with the proviso that the amino acid sequence is not IGF-1, insulin, or fragments thereof, and a pharmaceutically acceptable carrier.

- 231. (Once Amended) The composition according to claim 230, wherein the peptide comprises the amino acid sequence NFYDWFV (SEQ ID NO: 2435).
- 232. (Once Amended) The pharmaceutical composition according to claim 230, wherein the peptide comprises the amino acid sequence QMKDIFYSLLASLAA (SEQ ID NO: 2653).
- 233. A pharmaceutical composition comprising a amino acid sequence which binds specifically to IR receptor at Site 1 and is an insulin agonist, with the proviso that the amino acid sequence is not insulin, IGF, or fragments thereof, and a pharmaceutically acceptable carrier.
- 234. (Once Amended) The pharmaceutical composition according to claim 233, wherein the peptide comprises the amino acid sequence FYDWF (SEQ ID NO: 2411).
- 235. (Once Amended) The pharmaceutical composition according to claim 233, wherein the peptide comprises the amino acid sequence FYSLLASL (SEQ ID NO: 2651).
- 236. A method of treating diabetes comprising administering to an individual in need of treatment a therapeutically effective amount of an amino acid sequence which binds IR at Site 1 and is an insulin agonist, with the proviso that the amino acid sequence is not insulin, IGF, or fragments thereof.
- 237. The method according to claim 236 wherein the amino acid sequence is expressed by a recombinant vector administered to the individual.

238. The method according to claim 236 wherein the amino acid sequence is administered to the individual as a polypeptide.
239. A method of treating a patient with an IGF sensitive tumor comprising administering to an individual in need of treatment a therapeutically effective amount of an amino acid sequence which is an IGF-1R antagonist, with the proviso that the amino acid sequence is not insulin, IGF, or fragments thereof.
240. The method according to claim 239 wherein the amino acid sequence is expressed by a recombinant vector administered to the individual.
241. The method according to claim 239 wherein the amino acid sequence is administered to the individual as a polypeptide.
242. A method of screening for a compound which binds to IR comprising:
- i) immobilizing IR, or a fragment thereof, on a surface;
  - ii) incubating the IR, or fragment thereof, with a known amount of labeled amino acid sequence of Formulas 1-10, or an amino acid sequence selected from Figures 10-11, which binds IR and a compound to be screened under conditions which provide for binding of the labeled amino acid sequence to bind IR;
  - iii) measuring the amount of labeled amino acid sequence bound to IR;
  - iv) determining from the amount of bound labeled peptide whether the compound has competitively bound to IR.

243. An amino acid sequence capable of binding to Site 1 or Site 2 of IR identified by the method according to claim 242, with the proviso that the amino acid sequence is not insulin, IGF, or fragments thereof.
244. The amino acid sequence according to claim 243 wherein the amino acid sequence is an IR agonist.
245. The amino acid sequence according to claim 243 wherein the amino sequence binds to Site 1 of IR.
246. The amino acid sequence according to claim 243 wherein the amino sequence binds to Site 2 of IR.
247. A method of screening for a compound which binds to IGF-1R comprising:
- i) immobilizing IGF-1R, or a fragment thereof, on a surface;
  - ii) incubating the IGF-1R, or fragment thereof, with a known amount of labeled amino acid sequence of Formulas 1-9, or an amino acid sequence selected from Figure 10, which binds IGF-1R and a compound to be screened under conditions which provide for binding of the labeled amino acid sequence to bind to IGF-1R;
  - iii) measuring the amount of labeled amino acid sequence bound to IGF-1R;
  - iv) determining from the amount of bound labeled peptide whether the compound has competitively bound to IGF-1R.

248. An amino acid sequence capable of bind to Site 1 or Site 2 of IGF-1R identified by the method according to claim 247, with the proviso that the amino acid sequence is not insulin, IGF, or fragments thereof.
249. The amino acid sequence according to claim 248 wherein the amino acid sequence is an IGF agonist.
250. The amino acid sequence according to claim 248 wherein the amino sequence binds to Site 1 of IGF-1R.
251. The amino acid sequence according to claim 248 wherein the amino sequence binds to Site 2 of IGF-1R.
252. (Once Amended) An amino acid sequence comprising the sequence  $WX_{123}GYX_{124}WX_{125}X_{126}$  (SEQ ID NO: 2414) wherein  $X_{123}$  is proline, glycine, serine, arginine, alanine or leucine,  $X_{124}$  is any amino acid;  $X_{125}$  is a hydrophobic amino acid; and  $X_{126}$  is any amino acid.
253. The amino acid sequence according to claim 252 wherein  $X_{123}$  is proline and  $X_{125}$  is leucine or phenylalanine.
254. A recombinant peptide library comprising members wherein the majority of the members comprise an amino acid sequence of Formula 1.
255. A recombinant peptide library comprising members wherein the majority of the members comprise an amino acid sequence of Formula 2.



- 256. A recombinant peptide library comprising members wherein the majority of the members comprise an amino acid sequence of Formula 3.
- 257. A recombinant peptide library comprising members wherein the majority of the members comprise an amino acid sequence of Formula 4.
- 258. A recombinant peptide library comprising members wherein the majority of the members comprise an amino acid sequence of Formula 5.
- 259. A recombinant peptide library comprising members wherein the majority of the members comprise an amino acid sequence of Formula 6.
- 260. A recombinant peptide library comprising members wherein the majority of the members comprise an amino acid sequence of Formula 7.
- 261. A recombinant peptide library comprising members wherein the majority of the members comprise an amino acid sequence of Formula 8.
- 262. A recombinant peptide library comprising members wherein the majority of the members comprise an amino acid sequence of Formula 9.

263. A recombinant peptide library comprising members wherein the majority of the members comprise an amino acid sequence of Formula 10.